PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HKQ/PG4860	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06465	International filing date *(day/month/year)* 19.06.2003	Priority date *(day/month/year)* 19.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/195		
Applicant SB PHARMCO PUERTO RICO INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.12.2003	30.04.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albayrak, T Telephone No. +49 89 2399-7549

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06465

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-11	as originally filed

Claims, Numbers

12-15	as originally filed
1-11	filed with telefax on 14.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9-10 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 9-10 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-8, 11-15
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item I

Description, pages:

1-11 as originally filed

Claims, No.:

12-15 as originally filed

1-11 with telefax of 14/04/2004

Re Item III

1. The subject-matter of claims 9-10 is related to subject-matter considered to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4) (a) (i) PCT).

Re Item V

1. Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

   D2: WO 98 30537 A (BEAMS RICHARD MANSFIELD ;DRYSDALE MARTIN JAMES (GB); HODSON HAROLD) 16 July 1998 (1998-07-16)

2. The subject-matter of independent claim 1 relates to the preparation of solid pharmaceutical compositions comprising an antioxidant or a chelating agent, (2S)-2-amino-4-[2-(ethanimidoylamino)ethyl]thiobutanoic acid and a bulking agent.

3. The subject-matter of the present application appears to meet the criteria of Art. 33 (2) PCT.

   D2 discloses (2S)-2-amino-4-[2-(ethanimidoylamino)ethyl]thiobutanoic acid as active ingredient in pharmaceutical compositions containing anti-oxidants and several further agents which fall under the scope of the term "bulking agent" (see for example page 7 line 5 to page 8 line 9) but the compositions of D2 are no solid compositions.

The subject-matter of independent claim 1 differs from the disclosure of D2 in that the pharmaceutical compositions are solid compositions. Independent claim 1 therefore appears to meet the criteria of Art. 33(2) PCT.

Claims 2-14 are dependent on independent claim 1 and therefore appear to meet the criteria of Art. 33(2) PCT.

4. As for the inventive step the following comments apply:

Independent claim 1 differs from the disclosure of D2 in that the pharmaceutical compositions are solid dosage forms. From this technical feature no surprising/unexpected effect can be regarded.

Furthermore, the problem underlying the present application was the provision of stabilized, solid pharmaceutical compositions. The solution, according to the applicant lay in the provision of pharmaceutical compositions comprising (2S)-2-amino-4-[2-(ethanimidoylamino)ethyl]thiobutanoic acid a chelating agent and/or an antioxidant.
A preferred chelating agent is EDTA which is known to those skilled in the art as a complexing agent which is widely used to stabilize pharmaceutical compositions.
Antioxidants as maleic acid or ascorbic acid are known to those skilled in the art for the same purpose.

The discovery of an unrecognised problem may, in certain circumstances give rise to patentable subject-matter in spite of the fact that the claimed solution is retrospectively trivial and in itself obvious.
However, the posing of a new problem does not represent a contribution of inventive merits of the solution if it could have been posed by the average person skilled in the art. It also has to be taken into consideration that it is the normal task of the skilled person to be constantly occupied with the elimination of deficiencies, the overcoming of drawbacks and the achievement of improvements of known products.
Addressing a problem simply by looking for ways of overcoming difficulties arising from routine work, does not constitute inventiveness.
The appreciation of conventional technical problems which formed the basis of normal activities of the notional skilled person in the art, such as the removal of shortcomings or the optimisation of parameters can not involve an inventive step. The appreciation of a technical problem can only contribute to an inventive step in very exceptional circumstances.

The "problem" of low stability of the compound in solid dosage forms would immediately have been recognized by the skilled person from routine work and the overcoming of this problem by the addition of extremely well known

stabilizers to the pharmaceutical compositions in order to improve their stability can only be regarded as an apparent solution to the skilled person.

No feature in any of the claims appears to relate to a problem which would not have been immediately apparent, or a non obvious solution.

It therefore appears, that the subject-matter of claims 1-15 does not fulfil the criteria of Art. 33 (3) PCT.

5. D1 of the ISR could become relevant in some contracting states.

Claims

1. A solid pharmaceutical composition for oral administration comprising (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio} butanoic acid, a pharmaceutically acceptable bulking agent and one or more antioxidants or chelating agents.

2. A pharmaceutical composition as claimed in claim 1 wherein the (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid is in the form of its (1:1) compound with phosphoric acid, or a solvate thereof.

3. A pharmaceutical composition as claimed in claim 1 or claim 2 wherein the solvate is a hydrate.

4. A pharmaceutical composition as claimed in claim 3 wherein the hydrate is the monohydrate.

5. A pharmaceutical composition as claimed in claim 3 wherein the hydrate is the trihydrate.

6. A pharmaceutical composition as claimed in any of claims 1 to 5 wherein the (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid comprises from about 0.1 to about 5% by weight, the pharmaceutically acceptable bulking agent comprises from about 80 to about 99.5% by weight, and the antioxidant, chelating agent, or mixture thereof comprises from about 0.005 to about 5% by weight, based on the dry weight.

7. A pharmaceutical composition as claimed in any of claims 1 to 6 wherein the antioxidants or chelating agents are selected from the group comprising EDTA, malic acid, ascorbic acid and mixtures thereof.

8. A pharmaceutical composition as claimed in any of claims 1 to 7 wherein the pharmaceutically acceptable bulking agent comprises microcrystalline cellulose, starch or a mixture thereof.

9. A method for the treatment or prophylaxis of a clinical condition in a mammal, such as a human, for which an inhibitor of nitric oxide synthase is indicated, which comprises administration of a pharmaceutical composition as claimed in any of claims 1 to 8.

10. A method as claimed in claim 9 wherein the clinical condition is selected from arthritis, asthma, rhinitis, chronic obstructive pulmonary disease, ileus, migraine, pain and irritable bowel syndrome.

11. A pharmaceutical composition as claimed in any of claims 1 to 8 for use in medical therapy.